

Rabies

Natural History

Rabies virus causes acute encephalitis in all warm-blooded hosts, including humans, and the outcome is almost always fatal. Although all species of mammals are susceptible to rabies virus infection, only a few species are important as reservoirs for the disease. In the United States, several distinct rabies virus variants have been identified in terrestrial mammals, including raccoons, skunks, foxes, and coyotes. In addition to these terrestrial reservoirs, several species of insectivorous bats are also reservoirs for rabies.

Domestic species accounted for 6.8% of all rabid animals reported in the United States in 2001. The number of reported rabid domestic animals decreased 2.4% from the 509 cases reported in 2000 to 497 in 2001.

In 2001, cases of rabies in cats increased 8.4%, whereas those in dogs, cattle, horses, sheep and goats, and swine decreased 21.9%, 1.2%, 1.9% and 70.0% respectively compared with those reported in 2000. Rabies cases in cats continue to be more than twice as numerous as those in dogs or cattle. Pennsylvania reported the largest number of rabid domestic animals (46) for any state, followed by New York (43).

In this century, the number of human deaths in the United States attributed to rabies has declined from 100 or more each year to an average of 1 or 2 each year. Two programs have been responsible for this decline. First, animal control and vaccination programs begun in the 1940's have practically eliminated domestic dogs as reservoirs of rabies in the United States. Second, effective human rabies vaccines and immunoglobins have been developed.

In 2001, 49 states, the District of Columbia, and Puerto Rico reported 7,437 cases of rabies in animals and no cases in humans to CDC (Hawaii is the only state that has never reported an indigenously acquired rabies case in humans or animals). The total number of reported cases increased by 0.92% from those reported in 2000 (7,369 cases).

Transmission

Transmission of rabies virus usually begins when infected saliva of a host is passed to an uninfected animal. Various routes of transmission have been documented and include contamination of mucous membranes (i.e., eyes, nose, and mouth), aerosol transmission, and corneal transplantations. The most common mode of rabies virus transmission is through the bite and virus-containing saliva of an infected host.

Following primary infection, the virus enters an eclipse phase in which it cannot be easily detected within the host. This phase may last for several days or months. Investigations have shown both direct entry of virus into peripheral nerves at the site of infection and indirect entry after viral replication in non-nervous tissue (i.e., muscle cells). During the eclipse phase, the host immune defenses may confer cell-mediated immunity against viral infection because rabies virus is a good antigen. The uptake of virus into peripheral nerves is important for progressive infection to occur.

After uptake into peripheral nerves, rabies virus is transported to the central nervous system (CNS). Typically this occurs via sensory and motor nerves at the initial site of

infection. The incubation period is the time from exposure to onset of clinical signs of disease. The incubation period may vary from a few days to several years, but is typically 1 to 3 months. Dissemination of virus within the CNS is rapid. Active cerebral infection is followed by passive centrifugal spread of virus to peripheral nerves. The amplification of infection within the CNS occurs through cycles of viral replication and cell-to-cell transfer of progeny virus. Centrifugal spread of virus may lead to the invasion of highly innervated sites of various tissues, including the salivary glands. During this period of cerebral infection, the classic behavioral changes associated with rabies develop.

Signs and symptoms

The first symptoms of rabies may be nonspecific flu-like signs — malaise, fever, or headache, which may last for days. There may be discomfort or paresthesia at the site of exposure (bite), progressing within days to symptoms of cerebral dysfunction, anxiety, confusion, agitation, progressing to delirium, abnormal behavior, hallucinations, and insomnia. The acute period of disease typically ends after 2 to 10 days. Once clinical signs of rabies appear, the disease is nearly always fatal, and treatment is typically supportive. Disease prevention is entirely prophylactic and includes both passive antibody (immune globulin) and vaccine. Non-lethal exceptions are extremely rare. To date only six documented cases of human survival from clinical rabies have been reported and each included a history of either pre- or post-exposure prophylaxis.

Pathology

Pathology of rabies infection is typically defined by encephalitis and myelitis. Perivascular infiltration with lymphocytes, polymorphonuclear leukocytes, and plasma cells can occur throughout the entire CNS. Rabies infection frequently causes cytoplasmic eosinophilic inclusion bodies (Negri bodies) in neuronal cells, especially pyramidal cells of the hippocampus and Purkinje cells of the cerebellum. These inclusions have been identified as areas of active viral replication by the identification of rabies viral antigen.

Rabies vaccine and immune globulin

There is no treatment for rabies after symptoms of the disease appear. However, two decades ago scientists developed an extremely effective new rabies vaccine regimen that provides immunity to rabies when administered after an exposure (post-exposure prophylaxis) or for protection before an exposure occurs (pre-exposure prophylaxis). Although rabies among humans is rare in the United States, every year an estimated 18,000 people receive rabies pre-exposure prophylaxis and an additional 40,000 receive post-exposure prophylaxis.

Human rabies vaccine usually is well tolerated and adverse effects reported with the vaccines generally are mild or moderate adverse local or systemic effects. Serious systemic reactions have been reported rarely. Side-effects of vaccination against rabies include localized pain, swelling and erythema; rarely systemic effects include myalgia, malaise, headache, fever, and dizziness. Even rarer reactions include an immune complex-like reaction (<6%), allergic reactions, anaphylactic reactions (2 cases), and adverse nervous system effects. Because of the almost invariably fatal outcome of rabies, there are no known contraindications to post-exposure rabies vaccination when such prophylaxis is indicated. There also are no known

contraindications to pre-exposure rabies vaccination other than situations such as moderate or severe acute illness.

Pre-exposure prophylaxis

Pre-exposure vaccination is recommended for persons in high-risk groups, such as veterinarians, animal handlers, abattoir workers, and certain laboratory workers. Other persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk of having rabies should also be considered for pre-exposure prophylaxis. In addition, international travelers likely to come in contact with animals in areas of enzootic dog rabies which lack immediate access to appropriate medical care, including biologics, should be considered for pre-exposure prophylaxis.

People who work with live rabies virus in research laboratories or vaccine production facilities are at the highest risk of inapparent exposures. Such persons should have a serum (blood) sample tested for antibody every 6 months and receive booster vaccine, when necessary.

Purpose of pre-exposure prophylaxis

Pre-exposure prophylaxis is given for several reasons. First, although pre-exposure vaccination does not eliminate the need for additional medical attention after a rabies exposure, it simplifies therapy by eliminating the need for human rabies immune globulin (HRIG) and decreasing the number of vaccine doses needed – a point of particular importance for persons at high risk of being exposed to rabies in areas where immunizing products may not be available, and it minimizes adverse reactions to multiple doses of vaccine. Second, it may enhance immunity in persons whose post-exposure therapy might be delayed. Finally, it may provide protection to persons with inapparent exposures to rabies.

Pre-exposure prophylaxis regimen

Pre-exposure prophylaxis consists of three doses of rabies vaccine given on days 0, 7, and 21 or 28.

Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) is indicated for persons possibly exposed to a rabid animal. Possible exposures include animal bites, or mucous membrane contamination with infectious tissue, such as saliva. PEP should begin as soon as possible after an exposure. There have been no vaccine failures in the United States (i.e. someone developed rabies) when PEP was given promptly and appropriately after an exposure.

Administration of rabies PEP is a medical urgency, not a medical emergency. Physicians should evaluate each possible exposure to rabies and as necessary consult with local or state public health officials regarding the need for rabies prophylaxis.

Post-exposure prophylaxis regimen

In the United States, PEP consists of a regimen of one dose of immune globulin and five doses of rabies vaccine over a 28-day period. Rabies immune globulin and the first dose of rabies vaccine should be given as soon as possible after exposure. Additional doses of rabies vaccine should be given on days 3, 7, 14, and 28 after the

first vaccination. Current vaccines are relatively painless and are given in your arm, like a flu or tetanus vaccine.

What to do after a possible exposure

If you are exposed to a potentially rabid animal, wash the wound thoroughly with soap and water, and seek medical attention immediately. A health care provider will care for the wound and will assess the risk for rabies exposure. The following information will help your health care provider assess your risk:

- the geographic location of the incident
- the type of animal that was involved
- how the exposure occurred (provoked or unprovoked)
- the vaccination status of animal
- whether the animal can be safely captured and tested for rabies

Steps taken by the health care practitioner will depend on the circumstances of the bite. Your health care practitioner should consult state or local health departments, veterinarians, or animal control officers to make an informed assessment of the incident and to request assistance. The important factor is that you seek care promptly after you are bitten by any animal.

Public health importance of rabies

Over the last 100 years, rabies in the United States has changed dramatically. More than 90% of all animal cases reported annually to CDC now occur in wildlife; before 1960 the majority was in domestic animals. The principal rabies hosts today are wild carnivores and bats. The number of rabies-related human deaths in the United States has declined from more than 100 annually at the turn of the century to one or two per year in the 1990's. Modern day prophylaxis has proven nearly 100% successful. In the United States, human fatalities associated with rabies occur in people who fail to seek medical assistance, usually because they were unaware of their exposure.

Cost of rabies prevention

Although human rabies deaths are rare, the estimated public health costs associated with disease detection, prevention, and control have risen, exceeding \$300 million annually. These costs include the vaccination of companion animals, animal control programs, maintenance of rabies laboratories, and medical costs, such as those incurred for rabies post-exposure prophylaxis (PEP).

Accurate estimates of these expenditures are not available. Although the number of PEPs given in the United States each year is unknown, it is estimated to be about 40,000. When rabies becomes epizootic or enzootic in a region, the number of PEPs in that area increases. Although the cost varies, a course of rabies immune globulin and five doses of vaccine given over a 4-week period typically exceeds \$1,000. The cost per human life saved from rabies ranges from approximately \$10,000 to \$100 million, depending on the nature of the exposure and the probability of rabies in a region.